L16: Entry 11 of 29 File: USPT Apr 21, 1998

DOCUMENT-IDENTIFIER: US 5741519 A
TITLE: The production of active substance compositions in the form of a solid solution of the active substance in a polymer matrix, and active substance compositions produced by this process

BSPR:
Melt extrusion processes for producing drug forms (tablets, pellets, granules) are described in the literature. The combination of an extrusion step with a subsequent shaping step, in particular, makes this process a very straightforward, because single-stage (and thus cost-saving), method for producing drug forms such as tablets (DE-A-1 766 546 and U.S. Pat. No. 4,880,585). These and other references (EP-A-580 860) mention that the thermal processing during the extrusion cause the active substance, owing to the melting, to be incorporated in the form of a molecular dispersion into the likewise molten polymer melt. This is manifested by the fact that clear transparent melts containing active substances are formed, and these usually do not recrystallize after these compositions have been cooled to room temperature, but on the contrary maintain their molecular dispersion.

BSPR:
Formulations which contain the active substance in nonionic form are, however, disadvantageous in many cases, because it is often only the corresponding salts of the active substance which have sufficient solubility in the aqueous medium. This means that although there is rapid release of the (molecular) active substance from the solid solutions in the drug form (eg. tablets), there is in this case no release of a salt which is readily soluble in water, so that recrystallization may rapidly occur. However, sufficient solubility in water is indispensable inter alia to make satisfactory absorption possible.

BSPR:
In a few cases it is also possible for the novel process to be used to make active substances which have hitherto been administered predominantly in their nonionic form more bioavailable by specific salt formation. One example of this is the active substance ibuprofen, which carries a (protonated) carboxyl group. Ibruprofen is employed for the therapy of pain, which generally requires a rapid onset of action (eg. headache tablet). However, the precondition for rapid display of the action is that the active substance rapidly dissolves after oral administration (eg. after taking a tablet) so that the following absorption can take place rapidly. Thus, preparations with a high rate of dissolution of the active substance are advantageous in this case. Solid solutions based on the nonionic active substance, which even on their own contribute to rapid solubilization, are described in the literature (EP-A-580 860). However, these preparations have disadvantages because the active substance is present in the nonionic form which has low solubility in water, which in fact makes it possible to prepare the solid solutions. On the other hand, the salts with better solubility in water are required for rapid therapy.

BSPR:
These previously disclosed formulations based on solid solutions can be improved by using the process according to the invention via specific salt formation because ibuprofen salts have better solubility in water than the nonionic active substance. This increases the rate of release of active substance from the drug form (eg. tablet), as can easily be shown by the in vitro release method conventional for this purpose.

BSPR:
The preparations according to the invention are produced in conventional processes, preferably in single or twin screw extruders, with particular preference for corotating twin screw extruders because their mixing action is more intensive. Shaping of the melts containing active substance can take place in a variety of ways. Direct melt calendering, for example to tablets, is possible as described in EP-A 240 906. It is likewise possible to produce pellets by cutting thin extrudates with rotating knives as described in DE-A 38 30 355. Both processes have the advantage that they can be carried out continuously and directly after the extrusion step (quasi on-line). However, it is also possible to allow the extruded melts to cool and only then to carry out further steps for shaping, eg. milling to granules which can be used for instant drinks or which can be packed in hard gelatin capsules or compressed to tablets. The compositions according to the invention are generally employed as drugs. However, it is also possible to process active substances which are known, for example, for the treatment of plant diseases and for eradicating insects by the process according to the invention. Active substances for the purpose of the process according to the invention also include vitamins and minerals (eg. trace elements).

DEPR:
A powder mixture consisting of 20.0% by weight of ibuprofen (nonionic) and 80% by weight of vinylpyrrolidone/vinyl acetate copolymer (Kollidon VA-64 (BASF)) was extruded in a twin screw extruder (ZSK-30, Werner and Pfleiderer) to give a clear transparent melt. The melt was compressed immediately after leaving the extruder to oblong tablets weighing about 1000 mg with the aid of a molding calender by the process disclosed in U.S. Pat. No. 4,880,585. The extrusion conditions were set as follows:

DEPR:
Release of active substance from these tablets was determined by the USP paddle method

DEPR:
The release of active substance from the oblong tablets weighing about 1000 mg obtained as in Example 1 was determined by the same method:

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI	5290569.pn. and cyclodextrin	2	L30
USPT,PGPB,JPAB,EPAB,DWPI	4880585.pn.	3	L29
USPT,PGPB,JPAB,EPAB,DWPI	127 and (lactose or mannitol or sugar or sucrose)	255	L28
USPT,PGPB,JPAB,EPAB,DWPI	125 and (tablet or pills)	309	L27
USPT,PGPB,JPAB,EPAB,DWPI	125 and 18	23	L26
USPT,PGPB,JPAB,EPAB,DWPI	12 not carboxylic	705	L25
USPT,PGPB,JPAB,EPAB,DWPI	14 and 18	20	L24
USPT,PGPB,JPAB,EPAB,DWPI	119 and 18	30	L23
USPT,PGPB,JPAB,EPAB,DWPI	121 and tablet$	271	L22
USPT,PGPB,JPAB,EPAB,DWPI	119 not 220	379	L21
USPT,PGPB,JPAB,EPAB,DWPI	14 and calender$	6	L20
USPT,PGPB,JPAB,EPAB,DWPI	12 same (mannitol or sucrose or xylitol or sugar or lactose)	453	L19
USPT,PGPB,JPAB,EPAB,DWPI	12 and (mannitol or sucrose or xylitol or sugar or lactose)	739	L18
USPT,PGPB,JPAB,EPAB,DWPI	4880585.pn.	3	L17
USPT,PGPB,JPAB,EPAB,DWPI	112 and (tablets or pills)	29	L16
USPT,PGPB,JPAB,EPAB,DWPI	112 and (solid)	527	L15
USPT,PGPB,JPAB,EPAB,DWPI	112 and ROSENBERG	14	L14
USPT,PGPB,JPAB,EPAB,DWPI	112 and 18	2	L13
USPT,PGPB,JPAB,EPAB,DWPI	(melt or mold$ or mould$) adj1 calender$	1231	L12
USPT,PGPB,JPAB,EPAB,DWPI	110 and ($cyclodextrin or cyclodextrin)	74	L11
USPT,PGPB,JPAB,EPAB,DWPI	18 and ((process or method) adj2 (making or producing))	1169	L10
USPT,PGPB,JPAB,EPAB,DWPI	18 and 12	40	L9
USPT,PGPB,JPAB,EPAB,DWPI	solid adj1 dosage adj1 form	5008	L8
USPT,PGPB,JPAB,EPAB,DWPI	14 and (process adj2 making)	5	L7
USPT,PGPB,JPAB,EPAB,DWPI	14 and (molding)	11	L6
USPT,PGPB,JPAB,EPAB,DWPI	14 and (molding adj1 calendar)	0	L5
USPT,PGPB,JPAB,EPAB,DWPI	13 not carboxylic	251	L4
USPT,PGPB,JPAB,EPAB,DWPI	12 same (mannitol or sugar or sucrose or lactose)	453	L3
USPT,PGPB,JPAB,EPAB,DWPI	cyclodextrin same ((polyethylene adj1 glycol) or (polyvinylpyrrolidone) or (vinyl adj1 acetate) or PVP or PEG)	1088	L2
USPT,PGPB,JPAB,EPAB,DWPI	cyclodextrin	12813	L1

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L27	L26 and (extrusion or extrudable)	34	L27
L26	L25 and tablet	486	L26
L25	L24 and (drug or active)	644	L25
L24	((polyvinylpyrrolidone or PVP) same cyclodextrin)	714	L24
L23	L22 and cyclodextrin	43	L23
L22	L21 and PVP	343	L22
L21	binder and (solid near dosage near form)	3681	L21
L20	6365188.pn. and (complex or umcomplex$)	1	L20
L19	4834985.pn. and extru$	0	L19
L18	4834985.pn. and extrusion	0	L18
L17	l15 and binders	40	L17
L16	L15 and (pvp or polyvinylpyrrolidone)	45	L16
L15	l13 and (extrusion or extrudable)	70	L15
L14	l13 and polyvinylpyrollidone	7	L14
L13	L12 and tablet	1627	L13
L12	l3 and pharmaceuticals	2966	L12
L11	l6 and (process near making)	95	L11
L10	l6 and (process of making)	929	L10
L9	l6 and (extrusion or extrudable or process)	885	L9
L8	l6 and (extrusion or extrudable)	85	L8
L7	l6 and (extrusionor extrudable)	1	L7
L6	L4 and (PVP or PEG or (polyethylene near glycol) or polyvinylpyrollidone)	1031	L6
L5	L4 and polyvinylpyrollidone	7	L5
L4	L3 and tablets	1853	L4
L3	cyclodextrin near (beta or alpha or gamma)	5927	L3
L2	L1 and tablets	33	L2
L1	cyclodextrin near esters	154	L1

END OF SEARCH HISTORY